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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,904	12/02/2003	Kei Roger Aoki	16952CON1CIP3 (BOT)	4172

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STEPHEN DONOVAN
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,904	AOKI ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,29,47 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,29,47 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-1-07, 4-12-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-12-07 has been entered.

2. In the response filed with the RCE on April 12, 2007, Applicants amended the claims to read " a method for treating spastic muscle . . ." In amending the claimed invention, Applicants effectively changed invention from treatment of strabismus to treatment of pain with muscle activity and contracture. In that response Applicants canceled claim 3 and added 29-77.

In response to this Amendment, a notice of non responsive was mailed indicated that Applicants had switched inventions from treatment of strabismus to treatment of pain with muscle activity and contracture. In the response to the non-responsive amendment, Applicants filed an amendment on 9-15-07, amending the claims to recite a method for treating strabismus. Applicants have thus amended to the claims to the subject matter pending prior to the final rejection and the filing of the RCE. Claims 1, 5, 29 have been amended in this response, claims 29, 46 and 63 were added in the response dated 4-12-07. claims 1-2, 4-5, 29, 47, 63 are pending in this Application.

Priority Under 35 U.S.C. 119

3. Applicants request that priority to parent application 08/173,996 be granted since the parent application provide ample support for the claimed invention. Applicants state that the "parent

application fully describes the effective amount of the botulinum toxin free of complex protein (i.e. pure botulinum toxin) to treat strabismus." Applicants refer to pinpoint citations in the parent application as support for their contention. The parent application, it is asserted, discloses neurotoxic component of a botulinum toxin having molecular weight of about 150kDa "which can be useful in a method of present invention" and "conventional techniques are known in for culturing and purifying a botulinum toxin." Furthermore, with regards to dosage Applicants state that "determining the effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be strabismus in the present case) is well within the ordinary skill in the art."

Applicants arguments have been fully considered but have not been found persuasive and the priority to parent application 08/173,996 is hereby denied.

The MPEP states:

> The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the prior application and in the later-filed application must be **sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112.** See Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The prior-filed application must disclose the common named inventor's invention claimed in the later-filed application in the manner provided by the first paragraph of 35 U.S.C. 112. See 37 CFR 1.78(a)(1). Accordingly, the disclosure of the prior-filed application must provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph."

See MPEP 201.11. Thus, the parent application must comply with both written description and enablement under 35 U.S.C. 112 First Paragraph.

Lack of Enablement

The parent application also lacks an enabling disclosure for the use of imply pure toxin or toxin free of botulinum toxin complex protein. In response to the office action dated, 9-26-06, Applicants stated:

> "**At the time of the filing of the present application, one of ordinary skill would not consider the teachings of the Tse reference regarding the use of purified botulinum toxin to be relevant to clinical treatment, such as the treatment of cervical dystonia in humans**. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings, Specifically, Schantz et al. states:
>
> > Most recent information concerning the structure and pharmacology of botulinum toxin has been obtained with purified neurotoxins, but it is unlikely that these will be used in clinical settings. The toxin complexes are much more stable than neurotoxin and can be diluted and formulated with retention of toxicity. Pure neurotoxins can be kept for several weeks to months in solution in the cold but are inactivated on dilution, formulation, and drying.
>
> Schantz et al., Microbiological Reviews, Mar 1992, p. 80-99, 89, second column, emphasis added, Exhibit 2. Since it was believed at the time of filing the present application that purified botulinum toxin would not be effective for clinical use, one of ordinary skill would not be impelled to combine the teachings of the Tse reference (use of purified botulinum toxin in non-clinical settings, i.e., rat experiments) with the teachings of the Balkan/Han references (use of complexed botulinum toxin in clinical setting for treating strabismus in humans)."

Applicants parent Application was filed one year and eight months after the publication of Schantz reference. However, Applicants specification neither disclosed nor implied that pure toxin was clinically ineffective, as recited by the state of the prior art at time. The specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective. Given the state of the art as recited by Schantz, such information was **necessary and critical** to allow one of ordinary skill in the art to use pure toxin in a clinical setting. Without such guidance,

one would be burdened with undue experimentation to practice the claimed invention. For the dosage, Applicants have stated that determining the effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be strabismus in the present case) is well within the ordinary skill in the art. However, given the teaching of Schantz, it is unclear how one would go about determining the effective amount. The parent application does not provide any guidance in this manner. Thus, since the parent application does not provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph, the priority is denied for 08/173,996.

Response to Applicants arguments

The priority under 35 U.S.C. 119 to parent application 08/173,996 and 08/627,118 has been denied for the reasons set forth in the previous office action and the reasons set forth below. It should be noted, however, that the basis for denial of priority is under 35 U.S.C. 112 First paragraph Enablement. Applicants arguments regarding the state of the prior art with respect to the 150kda component of the botulinum toxin has been found persuasive to over come the 112 First Paragraph Written Description. Applicants arguments establish that prior to Applicants filing date the 150kDa component was known in the art and could have been obtained by known methods. Further, the specification's disclosure that "[b]oth the single and dichain (forms of the neurotoxic component) are useful in the method of the present invention" are sufficient to overcome the Written Description issues. However, Applicants arguments have not overcome the 112 First Paragraph Enablement issues for the reasons set forth below.

Applicants argue that page 4 of the parent applications' specification discloses that botulinum toxin can be obtained by culture, fermentation, and purification in accordance with

known techniques. Applicants make reference to Hatheway et al., Wagman et al. and DasGupta et al. which teach how one can produce the 150kda portion of the botulinum toxin. Further, neurotoxic component was commercially available form several sources prior to the priority date of this application. Thus, the specification in light of the prior art clearly enables a person of ordinary skill in the art to obtain the neurotoxic component of a botulinum toxin without undue experimentation.

With respect to how to using the toxin, the specification state that both the single chain and dichain forms of the neurotoxin component are useful in the invention (see page 5 of the specification). The specification discloses particulars as to how to administer the toxin, where the phrase "the toxin" is used to mean either a botulinum toxin complex or a neurotoxic component. Applicants make reference to the Brin Declaration, by Dr. Brin, which states that a physician would have been able to "with little or no difficulty" obtain the neurotoxic component to use to treat sweating, since the toxin can be obtained commercially or purified from botulinum toxin complex. With respect to the state of the art and Schantz specifically, Applicants state that the office action has misunderstood and mischaracterized the teaching of Schantz. Schantz disclosure indicates that a long felt need for other botulinum toxin types for clinical use is necessary. Applicants state that the specification provides guidance and working examples such that one can obtain the botulinum toxin, purify, stabilized and preserve the toxin. The state of the art was such that one of ordinary skill in the art could obtain the toxin from known techniques. Applicants state that "it was well known to the prior art that the neurotoxic component is the biologically component of a botulinum toxin. See Brin declaration. Therefore the predictability of therapeutic efficacy upon use of the neurotoxic component must be considered to be high or very predictable." Applicants conclude that "[I]t would appear that no experimentation would be required by one of ordinary skill to practice the

claimed invention because (a) it was known to the person of ordinary skill in 1993 that the neurotoxic component of a botulinum toxin could be obtained by simply running a botulinum toxin complex through a protein separation resin in an alkaline pH buffer and furthermore the neurotoxic component of a botulinum toxin was available for purchase simply by ordering it from a commercial supplier, such as Sigma. See Brin Declaration paragraph 18(a) and (b)."

The Declaration by Dr. Brin, the declaration states that "in my opinion a physician of ordinary ability with knowledge of or experience using botulinum toxin (the "physician") would in December 1993 have very clearly realized upon reading the '996 application that the '996 patent application describes methods for treating" the disorders claimed. The declaration states that the toxin component could be obtained by well known methods in the art. The declaration concludes that "upon reading the '996 application in Decmeber 1993, would have been able with little or no difficulty to obtain the neurotoxic component of a botulinum toxin so as to be able to use the neurotoxic component to treat a patient with on or more of the Disorders."

Applicants arguments have been fully considered but have not been found persuasive.

First Applicants response asserts repeatedly that one of ordinary skill in the art could make the 150 Kda component of the botulinum toxin. However, the rejection was based on the fact that the specification did not provide ample guidance on "how to use" the neurotoxic component in a clinical setting. Enablement requires that the invention be described in to such manner that one of ordinary skill in the art can make and use the invention. The "how to make" prong of the enablement is different form "how to use" prong of the enablement (see MPEP 2146.01(b) and 2146.01(c)). The mere fact that one of ordinary skill in the art can make a the invention does not imply nor provide insight in determining if one can use the invention. Applicants stated in their previous response, "**[A]t the time of the filing of the present application, one of ordinary**

skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . ." As Applicants response shows, the art knew how to make the purified toxin, yet Applicant still concluded the art did not provide guidance as how one could use the purified botulinum toxin component in a clinical setting.

Applicants state that the Schantz was applied to rebut a rejection under obviousness, thus implying that the standards of enablement for a reference in the obviousness setting are different than the standards under 112 first paragraph. Again, Applicants have not set forth a basis to demonstrate such a distinction. The standards to render a reference non-enabling are the same as the standards to render a specification non-enabling under 112 first paragraph. That is, both, require the same analysis the state of the prior art, the amount of guidance provided within reference, the presence of working examples etc. . ., to allow one to determine how to make and use the invention. Thus, Applicants cannot state that the conclusions made by them (e.g. "**[A]t the time of the filing of the present application, one of ordinary skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings**. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . .") are irrelevant in determining if their disclosure is enabled.

Applicants state that the disclosure provides working examples that use botulinum toxin and "botulinum toxin" in each of these examples encompasses use of the neurotoxic component, at least because as explained at page 2, lines 24-25 of the specification "The term Botulinum toxin is a generic term...." However, it is unclear how Applicants makes such a conclusion. The examples do

not provide any specificity with respect to using the neurotoxic component. **Applicants knew, at the time of filing, that the state of the art was that of Schantz. Yet Applicants disclosure neither disclosed nor implied that pure toxin was clinically ineffective, as taught by Schantz.** Further, Applicants did not provide any guidance to one of ordinary skill in the art how one could avoid the problems associated with purified butlinum toxin component. Rather, as Applicants stated, the disclosure simply gave a general teaching, since the term Botulinum toxin is a generic term, implying that the knowledge of what was known for the complexed toxin could be used for non-complexed toxin. In essence, in order to establish enablement, Applicants rely heavily on the state of the art. Yet when Schantz is forwarded as the state of the art as of 1993, Applicant deny such conclusions without forwarding any evidence to the contrary. As indicated by Schantz et al. the teachings of complexed toxin could not be utilized purified botulinum toxin since the purified potion is so labile that it would not be used in clinical settings.

Turning to Declaration, the Declaration does not provide any evidence to counter the contentions raised by Schantz et al. While one of ordinary skill in the art may be able to make the neurotoxic component the Declaration does not set forth how one of ordinary skill in the art can use the toxic component as claimed to treat the disorders as claimed "with little or no difficulty." The MPEP states "The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement." Here, the Declaration does not set forth any evidence, between the date of Schantz et al. and the filing date of the present invention, to rebut how at the time of the filing of the present application, one of ordinary skill would consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings, given that Schantz et al. clearly stated that

purified botulinum toxin is so labile that it would not be used in clinical settings. Thus, the declaration submitted is ineffective to overcome the rejection.

Since the specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective and given the state of the art as recited by Schantz, one would be burdened with undue experimentation to practice the claimed invention.
Thus, since the parent application does not provide enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph, the priority is denied for 08/173,996.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-2, 4-5, 29, 47, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Kohl et al. and Tse et al. and Aoki et al. (US 6,113,915) for the reasons set forth in the previous office action and the reasons set forth below.

Applicants argue that the rejection cannot be maintained since they are entitled to priority to December 28, 1993. If priority is granted Han and Aoki cannot be prior art. Second Applicants again assert that combination of the remaining references in the rejection, Anderson (1992) and Tse (1982), cannot render the amended claims obvious because Schantz, discloses on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting", thereby showing that the prior art teaches away from a combination of Tse with Anderson to thereby allegedly teach the claimed invention."

Applicants arguments have been fully considered but have not been found persuasive.

First, the priority issue has been addressed above. Since priority is still denied and the effective filing date is 5-21-03 (filing date of 10/443593), Han and Aoki et al. are prior art to the claimed invention. Secondly, with respect to Schantz et al. Kohl et al. teaches the administration of botulinum toxin NT-201, a highly purified botulinum toxin that consists of pure neurotoxin. The results showed that that the paralytic effect of appears to be faster with NT-201 based on 20% CMAP decline. The maximum effect of this toxin was comparable to the complexed neurotoxin (see page 165). Note that the subjects used were human male volunteers. Note that this reference was cited in Hunt (US2003/0118598), which has the same Assignment as the instant application, as the basis to conclude that pure botulinum toxin can be formulated into pharmaceutical formulations for human use. "[P]ure botulinum toxin has been used in humans. see e.g. Kohl A., et al., Comparison of the effect of botulinum toxin A Botox (R)) with the highly-purified neurotoxin

(NT201) in the extensor digitorum brevis muscle test, *Mov Disord* 2000;15(Suppl 3):165. Hence, a pharmaceutical composition can be prepared using a pure botulinum toxin." (see page 4, paragraph 043).

It should be noted that Aoki et al. teach that 150kda portion of the toxin can be obtained form botulinum toxin A-G (see col. 5, lines 1-25). Thus, it would have been obvious to use the 150kda portion of any of seven types of toxin for the treatment of cervical dystonia.

Rejection is maintained.

5. Claims 1-2, 4-5, 29, 47, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Khol et al. and Aoki et al. (US 6,113,915) and Aoki et al. (20010018415) for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a method of treating strabismus using therapeutically effective amount of neurotoxin component of the botulinum toxin free of botulinum toxin protein.

For this rejection Applicants argue that Aoki patent is not prior art with regards to the amended claims. Aoki 2001-018415 is a divisional application having the same specification and the same effective filing date as the '996 application, also cannot be prior art with regard to the amended claims. "Hence, if priority to the December 28, 1993 filing date of the '996 application is granted the rejection is obviated and renders moot [this] rejection."

Applicants arguments have been fully considered but have not been found persuasive.

The priority issue has been addressed above. Since priority is still denied and the effective filing date is 5-21-03 (filing date of 10/443593), both Aoki et al. references are prior art to the claimed invention.

Rejection is maintained.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

11/26/07
ANISH GUPTA
PRIMARY EXAMINER